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DIFFERENT ROTAMER POPULATIONS AROUND THE C-5–C-6 BOND FOR α- AND β-D-GALACTOPYRANOSIDES THROUGH THE COMBINED INTERACTION OF THE GAUCHE AND ANOMERIC EFFECTS: A 300-MHz ^{1}H-N.M.R. AND MNDO STUDY

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A 300-MHz ^{1}H-n.m.r. study of methyl 2,3,4-tri-*O*-methyl-α- (**1**) and -β-D-galactopyranoside 6-(dimethyl phosphate) (**3**), using various solvents, shows that the *gauche* (gg) rotamer populations about the C-5–C-6 bond are the same in all solvents, whereas those of the *gauche(trans)* (gt) and *trans(gauche)* (tg, O-5 and O-6 *trans*) rotamers are solvent dependent. The tg population increases with decreasing polarity of the solvent, which is attributed to an increased electrostatic repulsion between O-5 and O-6 in apolar solvents. The tg population of **3** is larger than that of **1** and the same difference is observed in the corresponding compounds (**2** and **4**) which have a trigonal-bipyramidal five-coördinated phosphorus (P^V) at position 6 and which have a higher electron density at O-6. These differences in rotamer populations are due to an effect additional to that of the coulombic effect between O-5 and O-6. That these differences are caused by a combination of the gauche and anomeric effects is supported by the finding that the tg population increases with increasing pK_a of the group at C-1. The results of the n.m.r. measurements (in CCl_4) are reproduced fairly accurately by MNDO calculations on model systems. The solvent dependence of the rotamer population around the C-5–C-6 bond is a good criterion for the assignment of the H-6*S*,6*R* resonances since, for galactopyranosides, $J_{5,6S}$ increases and $J_{5,6R}$ decreases as the polarity of the solvent decreases.

INTRODUCTION

The anomeric effect has gained widespread attention[1–7] and has been explained in several theoretical studies[8–11]. Although the molecular orbital (MO) description of stabilising orbital interactions is now preferred, there is still some ambiguity in the interpretation of the total energies obtained from the MO calculations. Analysis in terms of localised MO's suggests that the oxygen lone-pairs are different[12], and that the anomeric effect is part of the more general gauche effect, whereas the use of cannonical MO's predicts that the oxygen lone-pairs are different[13]. Research in this area is still in progress, as the recent publication of two new theories shows[14,15]

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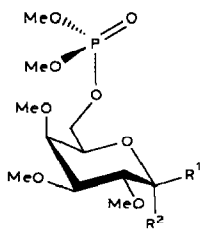
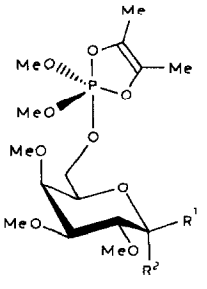
One of the major accomplishments of the MO theory is the quantitative description of the shortening of the C-1–O-1 bond first observed in the crystal structures of pyranosides[16] and attributed to the anomeric effect. Later, a correlation was noticed[17] between the pK_a of the group at the anomeric centre and the lengths of the endo- (O-5–C-1) and exo-cyclic (C-1–O-1) bonds. As the pK_a increases, the length of the O-5–C-1 bond increases, whereas that of the C-1–O-1 bond decreases. Also, the length of the endo-cyclic bond of β-pyranosides, where the C-1 substituent is equatorial, is larger than that in the corresponding α anomers. These changes in bond lengths can be interpreted as a combination of coulombic and stereoelectronic effects (principally the maximalisation of orbital-overlap[8]).

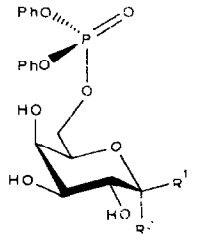
We have shown[18] that the conformation around the C-5–C-6 bond of methyl 2,3,4-tri-*O*-methyl-α-D-galactopyranoside 6-(dimethyl phosphate) (**1**) changes towards a higher *trans(gauche)* (**13** tg) population on going from four-coördinated phosphorus (6-P^{IV}) in **1** to the five-coördinated phosphorus (6-P^{V}) in **2**.



1 $R^1 = H, R^2 = OMe$
3 $R^1 = OMe, R^2 = H$

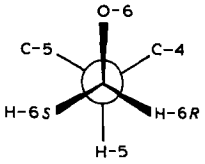


2 $R^1 = H, R^2 = OMe$
4 $R^1 = OMe, R^2 = H$



	R^1	R^2
5	H	OMe
6	H	*p*-OPh-NO_2
7	OMe	H
8	OPh	H
9	*p*-OPh-NO_2	H
10	*o*-OPh-NO_2	H

The observed rotamer distributions around the C-5–C-6 bond of **1** and **2** were also interpreted as a combination of a stereoelectronic (gauche) effect[12] and of coulombic repulsion between O-5 and O-6. In a P^V trigonal-bipyramidal structure (**2**), the electron density at O-6 is increased, thus favouring the tg rotamer **13** where O-5 and O-6 have maximal separation. The endo-cyclic oxygen O-5 is involved in both the change in the length of the O-5–C-1 bond and the conformational change around the C-5–C-6 bond. We then wondered whether stereoelectronic effects of the anomeric group are transmitted *via* O-5, thus influencing the conformation around the C-5–C-6 bond. We now show that, in the β anomers (**3** and **4**) of **1** and **2**, the tg population increases and that the conformation around the C-5–C-6 bond reflects the pK_a of the anomeric substituent.



gg

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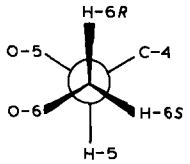

gt

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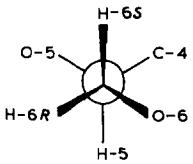

tg

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RESULTS AND DISCUSSION

In a 300-MHz ^{1}H-n.m.r. study of the galactopyranosides **3–10**, the contributions of the three staggered rotamers gg (**11**), gt (**12**), and tg (**13**) to the conformation around the C-5–C-6 bond were calculated using the following three equations which are based on an empirically generalised Karplus-relation[19], as used in previous studies[18].

$$x(\mathrm{gg}) = -0.075\,J_{5,6S} - 0.100\,J_{5,6R} + 1.303$$
$$x(\mathrm{gt}) = -0.054\,J_{5,6S} + 0.104\,J_{5,6R} + 0.061$$
$$x(\mathrm{tg}) = 0.129\,J_{5,6S} - 0.003\,J_{5,6R} - 0.364$$

The outcome of the calculations critically depends on a correct assignment of the H-6*S* and H-6*R* resonances, a problem which has not yet been settled. Therefore, the assignments of H-6*S*,6*R* were based on literature data, especially for compounds[20] that were specifically deuterated at C-6, and on the solvent dependence of the conformation around the C-5–C-6 bond. For phosphorylated nucleosides and tetrahydrofuran derivatives, the tg rotamer population around the C-4–C-5 bond increases with decreasing solvent polarity[21]; this is attributed to an increase in electrostatic repulsion between O-5′ and O-1′. A similar dependence was found for phosphorylated galactopyranosides (see below). In favourable cases, an unambiguous assignment was possible, *e.g.*, for methyl 2,3,4-tri-*O*-methyl-β-D-galactopyranoside in $CDCl_3$ where line-broadening of the H-6*S* resonance occurs due to hydrogen-bonding of HO-6 with O-5. This hydrogen bond results in an additional coupling with H-6*S* and no coupling with H-6*R* because of the unfavourable angle between HO-6 and H-6*R*. In Fig. 1, the conformation around the C-5–C-6 bond is gt; hydrogen-bonding is also possible in the gg conformation (**11**), but this rotamer is strongly disfavoured in galactopyranosides due to 1,3-*syn*-diaxial interactions. Addition of water removes the line-broadening (see Fig. 1).

Solvent dependence of the conformation around the C-5–C-6 bond. — The spectral parameters and the rotamer populations for **1** and **3** given in Table I show that the tg rotamer population increases as the solvent polarity decreases and that there is an accompanying decrease in the gt population. Although the gt rotamer is more favoured energetically in polar solvents because of the gauche effect[12] (a

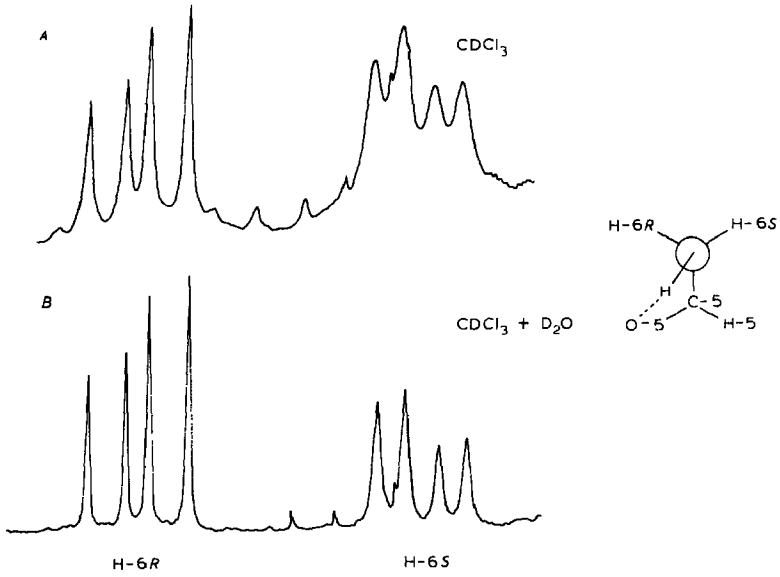


Fig. 1. H-6*R*,6*S* resonances for methyl 2,3,4-tri-*O*-methyl-β-D-galactopyranoside in *A*, $CDCl_3$; and *B*, $CDCl_3 + D_2O$.

pronounced preference of *gauche* over *trans* geometry in O–C–C–O fragments), the tg population in apolar solvents increases at the cost of the gt population because of an increased charge repulsion between O-5 and O-6. These results accord with those of Tvaroska and Kozar[23] on 2-methoxytetrahydropyran. The gg rotamer populations of **1** and **3**, to a good approximation, remain constant; in a theoretical study of the conformation of α- and β-D-glucopyranose, it was shown[24] that the tg rotamer is solvent dependent, despite a 1,3-*syn*-diaxial interaction of O-4 and O-6. The gg populations of **1** and **3** are independent of solvent polarity, despite the *gauche* orientations, since they are determined by steric factors rather than by electronic factors[18].

Although the solvent dependence of the rotamer populations (gg, gt, and tg) of **1** and **3** indicates the correctness of the assignment of the H-6*R*,6*S* resonances, the assignments were also established in a different way. Ohrui *et al.*[25] showed, by selective deuteration of C-6 involved in the glycosidic linkage, that for β-(1→6)-linked digalactosides, H-6*S* always resonated down-field of H-6*R* and stated that this result was "independent of the species of the protecting groups, and even of the conformational changes about the C-5–C-6 bond". Methyl 2,3,4-tri-*O*-methyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α- and -β-D-galactopyranoside were therefore prepared which only differ from **1** and **3** in that the 6-phosphate group is replaced by a 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl group. The solvent dependence of the rotamer populations around the C-5–C-6 interglycosidic bond of these disaccharides accorded with the results of Ohrui *et al.*[25] (large preference for the gt rotamer) and were virtually identical to those of the monosaccharides. Since

TABLE I

^{1}H-N.M.R. DATA AND THE CORRESPONDING C-5–C-6 ROTAMER POPULATIONS

Solvent	E_T[a]	*δ(H-6S)*	*δ(H-6R)*	$J_{5,6S}$	$J_{5,6R}$	*x(gg)*	*x(gt)*	*x(tg)*
Compound **1**								
CCl_4	32.5	4.249	4.186	5.97	6.72	0.18	0.43	0.39
$CDCl_3$	39.1	4.181	4.167	5.79	6.84	0.18	0.46	0.36
$(CD_3)_2CO$[b]	42.2	4.140	4.090	5.41	7.04	0.19	0.50	0.31
CD_3OD	55.5	4.201	4.164	4.83	7.62	0.18	0.59	0.23
D_2O	63.1	4.020	3.910	4.15	8.09	0.18	0.67	0.15
Compound **3**								
CCl_4	32.5	4.272	4.201	6.52	6.12	0.20	0.34	0.46
$CDCl_3$	39.1	4.210	4.194	6.20	6.83	0.16	0.43	0.41
$(CD_3)_2CO$	42.2	4.247	4.209	5.61	6.90	0.19	0.47	0.34
CD_3OD[c]	55.5	4.375	4.346	5.21	7.16	0.19	0.52	0.29
D_2O	63.1	4.012	3.952	4.66	8.11	0.14	0.65	0.21

[a]The solvent polarity parameter E_T is based on the position of electronic spectra peaks of pyridinium-*N*-phenolbetaine in various solvents[22]. [b]See ref. 18. [c]Obtained using a Bruker 500-MHz spectrometer at the Dutch National NMR Facility (Nijmegen).

the assignments for the disaccharides are unambiguous, the assignments of the H-6*R*,6*S* resonances for **1** and **3** (Table I) are established. The results for **1** and **3** are summarised in Fig. 2, and details for the disaccharides will be published elsewhere.

The data in Fig. 2 show that the tg rotamer population of the β compound **3** is always larger than that of the α compound **1**. This difference could reflect stereoelectronic effects, *e.g.*, a different orientation of orbitals along the C-1–O-5 bonds caused by the different orientation of the 1-substituent which, in turn, could influence the orbital interactions that govern the rotation around the C-5–C-6 bond. De Bruyn and Anteunis[26] suggested that the different $J_{5,6S(6R)}$ values for methyl α- and β-D-galactopyranoside might be caused by mutual repulsion of the dipoles associated with C-6–O-6 and C-1–O-1 bonds. However, this dipole–dipole interaction is probably weaker than the stereoelectronic effects involved[27]. Alternatively, the different rotamer populations of **1** and **3** might be attributed to different degrees of ring-puckering of these compounds. In general, the rings of α-pyranosides are less puckered than those of the β-pyranosides[28]; this results in a deviation from the proton-torsion angles (−60°, 60°, and 180°) for staggered conformations which we have used in the Karplus equation[18]. The neutron diffraction data for methyl α- and β-D-galactopyranoside[29] were used therefore to calculate two new sets of three equations, namely, α compounds: $x(\mathrm{gt}) = -0.052\,J_{5,6S} + 0.101\,J_{5,6R} + 0.056$; $x(\mathrm{tg}) = 0.125\,J_{5,6S} + 0.003\,J_{5,6R} - 0.351$; $x(\mathrm{gg}) = 1 - x(\mathrm{gt}) - x(\mathrm{tg})$; β compounds: $x(\mathrm{gt}) = -0.051\,J_{5,6S} + 0.098\,J_{5,6R} + 0.054$; $x(\mathrm{tg}) = 0.123\,J_{5,6S} + 0.006\,J_{5,6R} - 0.351$; $x(\mathrm{gg}) = 1\,x(\mathrm{gt}) - x(\mathrm{tg})$. Only the proton-torsion angles for the gt conformation

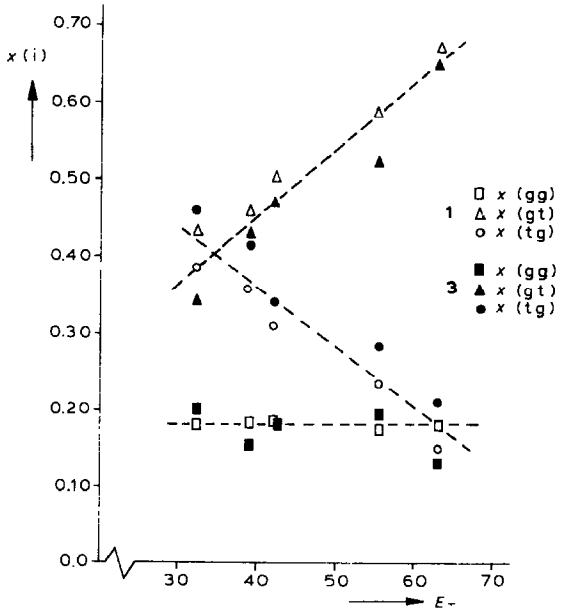
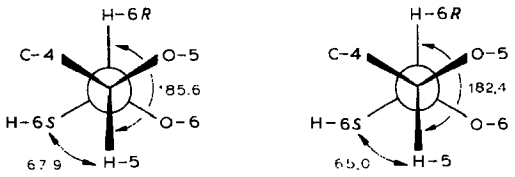


Fig. 2. Rotamer populations around the C-5–C-6 bond of **1** and **3**.

have been changed, as can be seen in the gt conformations **14** and **15** in which methyl α- and β-D-galactopyranoside crystallise. Because this conformer makes the largest contribution to the rotamer population around the C-5–C-6 bond (see Table I), the effect will be most noticeable from changes in the proton-torsion angles of the gt rotamer.



Insertion of the measured coupling constants (Table I) into these new equations gives a new set of rotamer populations for **1** and **3** [*e.g.*, in CD_3OD: for **1** $x(gg) = 0.16$, $x(gt) = 0.57$, $x(tg) = 0.27$; for **3** $x(gg) = 0.18$, $x(gt) = 0.49$, $x(tg) = 0.33$]. Although the absolute values of the rotamer populations for both **1** and **3** have changed, the differences in tg rotamer populations between the α and β compounds remains the same. Although this analysis is not based on the large number of crystallographic data necessary to obtain statistically reliable values for the proton-torsion angles of all rotamers around the C-5–C-6 bond for both α and β com-

TABLE II

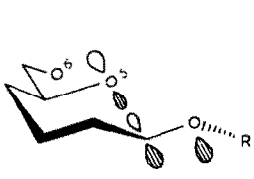
^{1}H-N.M.R. DATA FOR **5–10**

Compound	*Solvent*	*δ (p.p.m.)*		*J (Hz)*		
		H-6S	*H-6R*	*5,6S*	*5,6R*	*6S,6R*
5	CD_3OD	4.577	4.618	3.91	8.22	−10.59
6	CD_3OD	4.590	4.648	3.42	8.69	−10.93
7	CD_3OD	4.634	4.681	4.13	7.82	−10.72
8	CD_3OD	4.659	4.693	3.76	8.15	−10.71
8	$(CD_3)_2CO$	4.652	4.615	4.18	7.83	−10.62
9	CD_3OD	4.668	4.741	3.45	8.28	−10.86
10	CD_3OD	4.480	4.541	3.63	8.20	−10.81
10	$(CD_3)_2CO$	4.555	4.536	4.14	8.00	−10.73

pounds, it is sufficiently reliable to show that the observed differences in rotamer populations are not caused by differences in ring-puckering. This conclusion is supported by n.m.r. measurements on a series of acetylated methyl α- and β-D-glucopyranosides[30], where no difference was found in the $J_{5,6S(6R)}$ values for the α and β compounds, except for one compound for which there was probably hydrogen bonding between HO-6 and O-5. If the ring-puckering is the cause of the differences in rotamer populations for galactopyranosides, similar differences would be expected for glucopyranosides [different x(gg) and x(gt) values, equal x(tg) values]. Additional evidence that the difference is caused by stereoelectronic effects, and not by the ring-puckering, was obtained from the 300-MHz ^{1}H-n.m.r. data for **5–10** which are listed in Table II.

Relationship between $J_{5,6S}$ *and the* pK_a *of the group at C-1.* — The tg rotamer populations x(tg), which are largely indicated by the $J_{5,6S}$ values, are shown in Fig. 3. The changes in the length of the exo- and endo-cyclic bonds for the 1-*O*-acetyl, 1-*O*-phenyl, and 1-*O*-methyl derivatives are shown in Fig. 4 (ref. 31). Fig. 3. shows a clear trend towards decreasing x(tg) values with decreasing pK_a. The dotted lines in Fig. 3 are intended to show a trend and not a linear relationship, although such a relationship between the pK_a and the lengths of the C–O bonds around the anomeric centre has been demonstrated[17]. The correlation was accurate for the exo-cyclic bond of *trans*-1-oxadecalin systems (r = 0.9995) and reasonable for the endo-cyclic bond (r = 0.985). Later, it was shown for a series of 2-aryloxytetrahydropyrans that the dependence of the bond length on the pK_a of the group at the anomeric centre is different for equatorial and axial substituents, and is not necessarily linear[32]. Regardless of the exact relationship, there is a striking resemblance between the dependence of both the lengths of the C–O bonds and $J_{5,6S(6R)}$ [and x(tg)] on the pK_a (see Figs. 3 and 4). The fact that the lengths of the C–O bonds are determined by stereoelectronic interactions[8,31] favours the suggestion that the difference in rotamer populations for α- and β-D-galactopyranosides also has a

stereoelectronic origin. The ring-puckering cannot be responsible for the different conformations around the C-5–C-6 bond, since the J values for **8** and **9** are similar [**8** (MeOD): $J_{1,2}$ 7.74, $J_{2,3}$ 9.71, $J_{3,4}$ 3.38, $J_{4,5}$ 1.07 Hz; **9** (MeOD): $J_{1,2}$ 7.80, $J_{2,3}$ 9.74, $J_{3,4}$ 3.40, $J_{4,5}$ 1.10 Hz]. Thus, there seems to be a combined interaction of the anomeric and gauche effects which governs the rotation around the C-5–C-6 bond. This is visualised in **16** and **17** where the n–σ^* interaction (anomeric effect) and the σ_H–$\sigma_O{}^*$ interaction (gauche effect in the gt rotamer) are drawn for a β compound.



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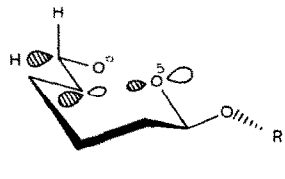

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The combined interaction of these two effects apparently results in a different stabilisation of the gt rotamer for α and β compounds. A more detailed description of these orbital interactions has been given by Kirby[31].

MNDO calculations. — The calculations were performed on **18** and **19** as models for α- and β-D-galactopyranosides, respectively. The value for ψ (C-2–C-1–O-1–Me) was restricted to 180°, the most stable conformation for the exo-cyclic methoxyl group in both the axial and equatorial conformation[5,31], and the energies

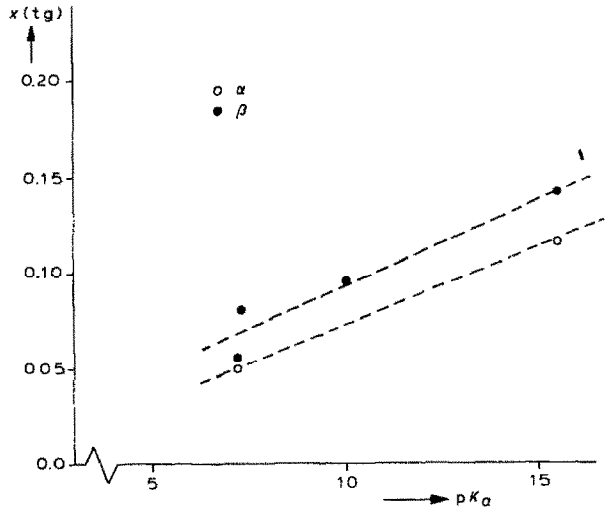


Fig. 3. The *trans(gauche)* populations of **5–10** [pK_a 7.15: **6** (○), **9** (●); pK_a 7.17: **10** (●); pK_a 10.0: **8** (●); pK_a 15.5: **5** (○), **7** (●)].

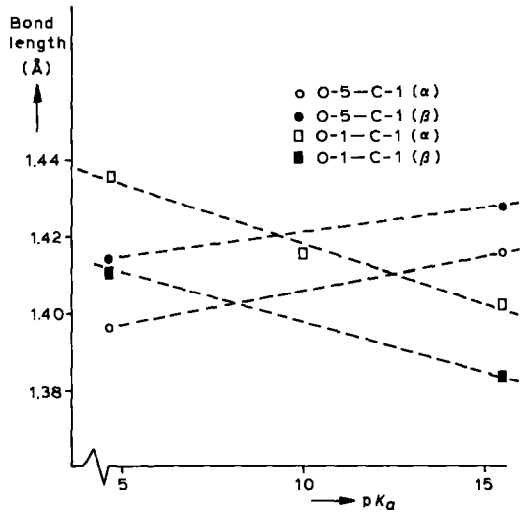
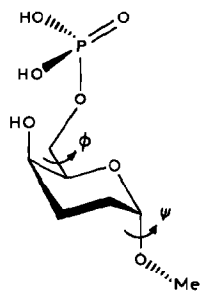


Fig. 4. Lengths of the exo- (O-1–C-1) and endo-cyclic (O-5–C-1) bonds of 1-*O*-acetyl (pK_a 4.75), 1-*O*-phenyl (pK_a 10.0), and 1-*O*-methyl (pK_a 15.5) derivates of glycopyranosides. Values for the lengths of the bonds are mean values for several structures and are taken from ref. 31.

for the staggered conformations around the C-5–C-6 bond (ϕ = C-4–C-5–C-6–O-6) were determined. All structures were optimised with respect to bond lengths, bond angles, and twist angles. As can be seen from the data in Table III, the anomeric effect does not lead to different electron densities on O-5 for α and β compounds. This finding accords with results obtained from PCILO calculations on 2-methoxytetrahydropyran[33] and STO-3G calculations on dimethoxymethane[34]. Hence, unlike[18] **1** and **2**, the different rotamer populations around the C-5–C-6 bonds in **1** and **3** cannot be attributed to differences in coulombic repulsion between O-5 and O-6. The relative energies of the different conformations of **18** and **19** are listed in Table IV, together with the calculated relative energies of the rotamers around the C-5–C-6 bond of **1** and **3**.



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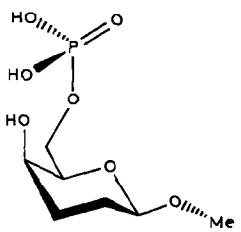

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TABLE III

ELECTRON DENSITIES FOR **18** AND **19**

Atom	**18**			**19**		
	ϕ			ϕ		
	−60 (gg)	*180 (gt)*	*60 (tg)*	*−60 (gg)*	*180 (gt)*	*60 (tg)*
O-5	−0.344	−0.355	−0.342	−0.350	−0.359	−0.344
O-6	−0.493	−0.524	−0.511	−0.495	−0.526	−0.509

TABLE IV

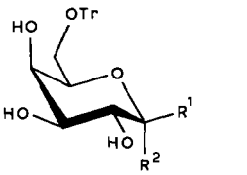
RELATIVE ENERGIES OF THE ROTAMERS AROUND THE C-5–C-6 BOND OF **1, 3, 18,** AND **19**

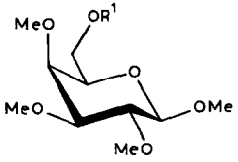
ϕ	**18**[a]	**19**[a]	**1**[b]	**3**[b]
−60 (gg)	1.26	4.70	0.50	0.49
180 (gt)	0.29	3.59	0.00	0.18
60 (tg)	0.00	3.40	0.07	0.00

[a]Energies relative to that of the tg rotamer of **18** (in kcal.mol^{-1}). [b]Free energy value (kcal.mol^{-1}) determined with the equation $\Delta G = -RT.\ln K$ for **1** and **3** (CCl_4).

The results in Table IV show that, whereas the calculations predict the tg rotamer to possess the lowest energy level for both α and β compounds, this is not found experimentally. The results for the β compound **3** in CCl_4 [the calculated anomeric effects for an isolated molecule are comparable with the experimental values in CCl_4 (*cf.* ref. 23)] are fairly good in that they predict both the correct order for the energy levels of the rotamers and the correct differences in energy of the tg and gt rotamers. The results for the α compound are not so good. In the calculations, the tg rotamer is favoured, whereas, experimentally, the gt rotamer is found to be more stable. However, the differences are small, and it should be kept in mind that the experimental rotamer populations are solvent dependent (see Table I), a fact that was not accounted for in the MNDO calculations. The calculations also predict a different E(tg) − E(gt) value for the α and β compounds **18** and **19**. The difference is small but of magnitude comparable to the experimental value (0.10 kcal.mol^{-1}) (see Table IV, footnote b). Thus, although the MNDO calculations give a fairly accurate qualitative description of the experimentally observed differences in rotamer populations for α- and β-D-galactopyranosides, a detailed analysis of the origin of this effect is probably not possible. It is likely that better results will be obtained with quantum-chemical calculations in combination with an investigation of the solvent effect by, for example, the continuum reaction-field method[23]. Recently, calculations with this method have been performed on α- and β-D-glucopyranose[24].

Influence of the substituents at positions 2–4 and 6. — A 300-MHz ^{1}H-n.m.r. study of the galactopyranosides **20–26** was carried out in order to investigate the influence of substituents at C-2,3,4,6 on the conformation around the C-5–C-6 bond of α- and β-D-galactopyranosides. The data are given in Table V and show that the substituents at C-2,3,4 strongly affect the $J_{5,6S(6R)}$ values, which range from $J_{5,6S}$ 3.30 Hz (**24**) for hydroxyl groups to $J_{5,6S}$ 5.99 Hz (**25**) for methoxyl groups. The $J_{5,6S}$ values were larger for the β compounds.





	R^1	R^2
20	H	OMe
21	OMe	H
22	H	*p*-NPh-Me
23	*p*-NPh—Me	H
24	o-OPh-NO_2	H

25 R^1 = Tr
26 R^1 = $(PhO)_2PO$

TABLE V

^{1}H-N.M.R. DATA FOR **20–26**

Compound	*CD_3OD*					*$(CD_3)_2CO$*				
	δ (p.p.m.)		*J (Hz)*			*δ (p.p.m.)*		*J (Hz)*		
	H-6S	*H-6R*	*5,6S*	*5,6R*	*6R,6S*	*H-6S*	*H-6R*	*5,6S*	*5,6R*	*6R,6S*
20	3.433	3.602	4.98	7.00	−9.68	3.386	3.514	5.13	6.86	−9.33
21	3.447	3.612	5.26	6.68	−9.56	3.386	3.537	5.35	6.70	−9.26
22	3.288	—	3.85	—	−9.86	3.243	3.572	3.90	7.76	−9.50
23	3.352	3.634	4.07	7.44	−9.86	3.228	3.433	7.51	5.99	−9.19
24	3.364	3.766	3.30	8.08	−10.07	3.160	3.471	7.91	5.65	−8.73
25	3.573	3.304	5.99	7.27	−9.36	3.490	3.253	6.05	6.94	−8.85
26	—	—	—	—	—	4.530	4.515	5.39	7.02	−10.32

The substituents at C-6 also influenced the rotamer population around the C-5–C-6 bond, as shown for compounds bearing the bulky trityl group (*cf.* **5** and **20**). However, the influence is not as pronounced as that of the substituents at C-2,3,4 (*cf.* **3**, **7**, and **26**). The influence of the O-6-P^V group of the β compound **4** on the rotamer population [$J_{5,6S}$ 7.29, $J_{5,6R}$ 6.07 Hz, x(tg) = 0.56] in comparison with the P^{IV} compound **3** [$J_{5,6S}$ 5.61, $J_{5,6R}$ 6.90 Hz, x(tg) = 0.34] shows that, due to

an increased electron density on O-6, the tg population increases, as found for **1** and **2**[18]. However, more important is comparison of **4** with the corresponding α-O-6–P^V compound **2** [$J_{5,6S}$ 6.92, $J_{5,6R}$ 5.90 Hz, x(tg) = 0.51][18] which shows that the tg population for the β compound **4** is higher, giving a difference similar to that found for the O-6–P^{IV} compounds **1** and **3** (see Table I). *Thus, the difference in rotamer populations around the C-5–C-6 bond for α and β compounds is the result of an effect additional to that of the coulombic effect between O-5 and O-6.* A similar conclusion was given by Wolfe *et al.*[8] for the variations in bond lengths in CH_2X_2 molecules. In general, it can be concluded that substituents at positions 2–4 and 6 affect the rotamer populations around the C-5–C-6 bond, equally for α- and β-D-galactopyranosides, and that the difference between α and β compounds is caused, presumably, by a combination of the gauche and anomeric effects.

Assignment of the H-6S and H-6R resonances. — Specific deuteration at C-6 enables assignment of the individual H-6*S*(6*R*) resonances[35], but there are few examples in the literature for galactopyranosides. For methyl α-D-galactopyranoside and its tetrabenzoate[20], the resonance of H-6*R* is down-field from that of H-6*S*. As can be seen from the data in Tables II and V, this situation is consistent with the assignment for all α and β compounds bearing hydroxyl groups at C-2,3,4 (**5–10** and **20–24**), except for **8** and **10** in $(CD_3)_2CO$. Although the reason for the two exceptions is not certain, it is probably attributable to an interaction with the solvent or a specific intramolecular interaction (*e.g.*, the reversal in the order of H-6*S* and H-6*R* chemical shifts for 4,6-di-*O*-acetylhexopyranoses[30]). The assignments in Tables II and V also accord with the algebraic relationship between $J_{6R,6S}$ and the tg rotamer population. An increase of $J_{6R,6S}$ reflects[36] an increase in the amount of the tg rotamer [*e.g.*, in CD_3OD: **7** $J_{6S,6R}$ −10.72 Hz, x(tg) = 0.14; **25** $J_{6R,6S}$ −9.36 Hz, x(tg) = 0.39]. The compounds (**1, 3, 25,** and **26**) bearing a methoxyl group at C-2,3,4 show a reversed pattern, with H-6*S* resonating down-field of H-6*R* (see Tables I and V). The value of $J_{5,6S}$ is smaller than that of $J_{5,6R}$ and the tg rotamer population is smaller than the gt population. Then, according to the "syn-upfield rule"[37], H-6*R* should resonate up-field of H-6*S*, which accords with experimental results. The apparent conflict with the "syn-upfield rule" for compounds with HO-4 axial was explained[26] by a superimposed deshielding effect of quasi-*syn*-axial O-4. Assuming that the assignments of H-6*S* and H-6*R* are correct, it can be seen from the data in Tables I, II, and V that the values for $J_{5,6S}$ tend to be larger in the less polar solvents. For $J_{5,6R}$, the reverse is true. Therefore, the solvent dependence of $J_{5,6R(6S)}$ of galactopyranosides seems to be a suitable criterion for the assignment of the H-6*S* resonances which can be used in combination with other criteria.

EXPERIMENTAL

Compounds **1, 2, 20** (all ref. 18) and **21** (ref. 38) were prepared according to literature procedures, and **25** was prepared according to the procedure for the

corresponding α compound[18]. The spectral data and melting points were in accordance with the expected structures. ^{1}H-N.m.r. spectra (300.1 MHz) were recorded in the F.t. mode with a Bruker CXP-300 spectrometer and a 32 K data set. Chemical shifts are given relative to the CHD_2COCD_3 quintet at δ 2.17, the CHD_2OD quintet at δ 3.49, or Me_4Si ($CDCl_3$) with an accuracy of ±0.05 Hz. Coupling constants in Tables I, II, and V were measured from expansions of the patterns, with an accuracy of ±0.1 Hz, and analysed using an iterative program[39]. ^{31}P-N.m.r. spectra (36.4 MHz) were recorded in the F.t. mode with a Bruker HX-90R spectrometer. Chemical shifts are related to external aqueous 85% H_3PO_4. ^{13}C-N.m.r. spectra (22.6 MHz) were recorded in the F.t. mode with a Bruker HX-90R spectrometer. Chemical shifts are related to the acetone septet (δ 30.7) or to Me_4Si ($CDCl_3$). Melting points were determined on a Mettler FP2 and are uncorrected. Optical rotations were determined with an AA10 polarimeter (Optical Activity Ltd.).

*Methyl 2,3,4-tri-*O*-methyl-β-*D*-galactopyranoside.* — Prepared from **25** by detritylation with chlorotrimethylsilane–sodium iodide[40], this compound had m.p. 72–74.5° (from ether), $[\alpha]_D$ −20.5° (*c* 1, methanol). N.m.r. data ($CDCl_3$): ^{1}H, δ 3.17 (dd, $J_{2,3}$ 9.70, $J_{3,4}$ 3.01 Hz, H-3), 3.33 (dd, $J_{1,2}$ 7.42, $J_{2,3}$ 9.70 Hz, H-2), 3.43 (m, H-5), 3.49 (dd, $J_{3,4}$ 3.01, $J_{4,5}$ 1.0 Hz, H-4), 3.527, 3.536, 3.564, and 3.589 (4 s, 4 OMe), 3.754 (m, H-6*S*), 3.922 (m, H-6*R*), 4.18 (d, $J_{1,2}$ 7.42 Hz, H-1); ^{13}C, δ 57.8–62.2 (4 OCH_3), 63.09 (C-6), 75.7, 76.7, 81.6, and 85.2 (C-2,3,4,5), 105.7 (C-1β).

*Methyl 2,3,4-tri-*O*-methyl-β-*D*-galactopyranoside 6-(dimethyl phosphate)* (**3**). — This compound was prepared by phosphorylation of methyl 2,3,4-tri-*O*-methyl-β-D-galactopyranoside with chlorodimethoxyphosphine and subsequent oxidation with ozone[41]. Column chromatography ($CHCl_3$–MeOH 95:5, R_F 0.57) gave the product as a viscous oil, $[\alpha]_D$ −9° (*c* 0.7, methanol). N.m.r. data [$(CD_3)_2CO$]: ^{1}H, δ 3.25 (dd, $J_{1,2}$ 7.59, $J_{2,3}$ 9.61 Hz, H-2), 3.36 (dd, $J_{2,3}$ 9.61, $J_{3,4}$ 2.98 Hz, H-3), 3.56 and 3.70 (2 d, $J_{P,OMe}$ 11.10 Hz, POMe), 3.60–3.87 (4 s, 4 OMe), 4.209 (m, H-6*R*), 4.247 (m, H-6*S*), 4.27 (d, $J_{1,2}$ 7.59 Hz, H-1); ^{13}C, δ 57.53, 59.28, 59.41, 61.49, 62.00, and 62.06 (6 OCH_3), 67.74 ($J_{P,OC}$ 5.2 Hz, C-6), 74.48 ($J_{P,OCC}$ 7.9 Hz, C-5), 76.71, 82.37, 85.68 (C-2,3,4), 106.19 (C-1β); ^{31}P, δ 6.394.

Anal. Calc. for $C_{12}H_{25}O_9P$: C, 41.86; H, 7.32. Found: C, 41.55; H, 7.77.

*2,2-Dihydro-2,2-dimethoxy-4,5-dimethyl-2-(methyl 2,3,4-tri-*O*-methyl-β-*D*-galactopyranosid-6-yloxy)-1,3,2-dioxaphosphole* (**4**). — This compound, prepared[18] from the phosphite (see **3**), was hygroscopic and could only be characterised by ^{1}H- and ^{31}P-n.m.r. spectroscopy. N.m.r. data [$(CD_3)_2CO$]: ^{1}H, δ 1.93 (s, 6 H, Me), 3.24 (dd, $J_{1,2}$ 7.14, $J_{2,3}$ 9.70 Hz, H-2), 3.30 (dd, $J_{2,3}$ 9.70, $J_{3,4}$ 2.97 Hz, H-3), 3.57 and 3.62 (2 d, $J_{P,OMe}$ 13.19 Hz, POMe), 3.54–3.73 (4 s, 4 OMe), 4.04 (m, H-6*S* and H-6*R*), 4.22 (d, $J_{1,2}$ 7.14 Hz, H-1); ^{31}P, δ −43.97.

Compounds **5**–**10**. — These compounds were prepared according to a literature procedure[42]. A typical example is outlined. To a solution of phenyl β-D-galactopyranoside (0.45 g) in dry pyridine (50 mL) at 0° was added slowly a solution of 0.5 equiv. of diphenyl phosphorochloridate in dry pyridine (5 mL); after 5 h,

more (0.5 equiv.) was added. The mixture was stirred at 25° for 15 h and then concentrated under reduced pressure, residual pyridine was removed by co-evaporation with toluene, and the resulting oil was purified by column chromatography (ethyl acetate, R_F 0.25). The resulting oil was triturated with ether to yield phenyl β-D-galactopyranoside 6-(diphenyl phosphate) (**8**) as a white powder (60 mg), m.p. 92–94.5°, $[\alpha]_D$ −25° (*c* 0.85, methanol). N.m.r. data [$(CD_3)_2CO$ plus 1 drop of MeOD to remove OH couplings]: ^1H, δ 3.80 (dd, $J_{2,3}$ 9.49, $J_{3,4}$ 3.42 Hz, H-3), 3.95 (dd, $J_{1,2}$ 7.68, $J_{2,3}$ 9.49 Hz, H-2), 4.10 (dd, $J_{3,4}$ 3.42, $J_{4,5}$ 1.20 Hz, H-4), 4.22 (m, H-5), 4.615 (m, H-6*R*), 4.652 (m, H-6*S*), 5.08 (d, $J_{1,2}$ 7.68 Hz, H-1), 7.1–7.6 (m, ArH); ^{13}C, δ 69.46 (C-4,6), 71.79 and 74.16 (C-2,3), 74.89 (C-5, $J_{P,OCC}$ 7.2 Hz), 102.29 (C-1β), 116.0–130.0 (aromatic); ^{31}P, δ −6.52.

Anal. Calc. for $C_{24}H_{25}O_9P$: C, 59.02; H, 5.16. Found: C, 59.17; H, 5.06.

The following compounds were prepared in this manner. Methyl α-D-galactopyranoside 6-(diphenyl phosphate) (**5**), m.p. 134–138.5°, $[\alpha]_D$ +26° (*c* 0.2, methanol). *p*-Nitrophenyl α-D-galactopyranoside 6-(diphenyl phosphate) (**6**), m.p. 110–114°, $[\alpha]_D$ +153° (*c* 0.7, methanol). Methyl β-D-galactopyranoside 6-(diphenyl phosphate) (**7**), obtained as a viscous oil, $[\alpha]_D$ −4.5° (*c* 0.5, methanol). *p*-Nitrophenyl β-D-galactopyranoside 6-(diphenyl phosphate) (**9**), m.p. 112–114.5°, $[\alpha]_D$ −56° (*c* 0.4, methanol). *o*-Nitrophenyl β-D-galactopyranoside 6-(diphenyl phosphate) (**10**), m.p. 107–109°, $[\alpha]_D$ −36° (*c* 0.6, methanol).

N-*(p-Methylphenyl)-6-O-trityl-α,β-D-galactopyranosylamine* (**22** *and* **23**). — These compounds were prepared by boiling under reflux a solution of 6-*O*-trityl-D-galactopyranose and *p*-toluidine in ethanol for 4 h. The resulting mixture was cooled to 0°, and the product was collected and recrystallised from ether–hexane to yield white crystals, m.p. 116–118°, which were shown by ^1H-n.m.r. spectroscopy to be a 1:4 αβ-mixture. Because the H-6*S*,6*R* signals of the α and β compounds were clearly separated (see Table IV), no further purification was attempted. The assignments of signals were proved by selective decoupling experiments. N.m.r. data [$(CD_3)_2CO$]: ^1H, δ 3.243 (m, H-6*S*α), 3.281 (m, H-6*S*β), 3.529 (H-6*R*β), 3.572 (H-6*R*α), 3.73 (dd, H-2β), 3.91 (m, $J_{4,5}$ 1.14 Hz, H-5β), 3.95 (dd, H-4β), 4.14 (dd, $J_{1,2}$ 5.25, $J_{2,3}$ 9.26 Hz, H-2α), 4.24 (m, H-5α), 4.63 (d, $J_{1,2}$ 8.38 Hz, H-1β), 5.18 (d, $J_{1,2}$ 5.25 Hz, H-1α), 6.8–7.6 (m, ArH).

Anal. Calc. for $C_{32}H_{33}NO_5$: C, 75.12; H, 6.50; N, 2.74. Found: C, 74.61; H, 6.60; N, 2.52.

o-*Nitrophenyl 6-O-trityl-β-D-galactopyranoside* (**24**). — *o*-Nitrophenyl β-D-galactopyranoside was stirred with 1 equiv. of trityl chloride in dry pyridine for 3 days at 25°. Evaporation of the solvent yielded a white powder which was purified by column chromatography ($CHCl_3$–MeOH 95:5, R_F 0.22), and then had m.p. 104–107.5° (from ether–hexane), $[\alpha]_D$ −35° (*c* 0.7, methanol). N.m.r. data [$(CD_3)_2CO$]: ^1H, δ 3.345 (dd, H-6*S*), 3.682 (dd, H-6*R*), 3.78 (dd, $J_{2,3}$ 9.43, $J_{3,4}$ 3.45 Hz, H-3), 3.96 (dd, $J_{3,4}$ 3.45, $J_{4,5}$ 1.15 Hz, H-4), 3.98 (dd, $J_{1,2}$ 7.68, $J_{2,3}$ 9.43 Hz, H-2), 4.16 (m, H-5), 5.23 (d, $J_{1,2}$ 7.68 Hz, H-1), 7.2–7.9 (ArH); ^{13}C, δ 65.7 (C-6), 71.0, 72.6, 75.4, and 76.7 (C-2,3,4,5), 103.2 (C-1β), 119.2–146.0 (aromatic).

Anal. Calc. for $C_{27}H_{29}NO_8$: C, 68.45; H, 5.38; N, 2.57. Found: C, 68.03; H, 5.87; N, 2.16.

Methyl 2,3,4-tri-O-methyl-β-D-galactopyranoside 6-(diphenyl phosphate) (**26**). — To a solution of methyl 2,3,4-tri-*O*-methyl-β-D-galactopyranoside (50 mg) and triethylamine (22 mg) in ether (10 mL) was added a solution of diphenyl phosphorochloridate in ether (3 mL). The mixture was stirred for 4 days at 25° and then concentrated. Column chromatography (ethyl acetate) of the oily residue gave **26**, $[\alpha]_D$ −6° (*c* 1.2, methanol). N.m.r. data [$(CD_3)_2CO$]: ^1H, δ 3.26–3.33 (m, H-2,3), 3.52, 3.56, 3.57, and 3.59 (4 s, 4 OMe), 3.78 (dd, $J_{3,4}$ 2.62, $J_{4,5}$ 1.18 Hz, H-4), 3.85 (m, H-5), 4.515 (m, H-6*R*), 4.530 (m, H-6*S*), 4.27 (d, $J_{1,2}$ 7.36 Hz, H-1), 7.3–7.6 (m, ArH); ^{13}C, δ 56.96, 58.94, 60.91, and 61.39 (4 s, 4 OCH_3), 68.77 (d, $J_{P,OC}$ 6 Hz, C-6), 73.98 (d, $J_{P,OCC}$ 7 Hz, C-5), 76.33, 82.07, and 85.41 (C-2,3,4), 106.22 (C-1β), 121.85–153.3 (aromatic); ^{31}P, δ −6.70.

Anal. Calc. for $C_{22}H_{29}O_9P$: C, 56.41; H, 6.24. Found: C, 56.31; H, 6.68.

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